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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/754,997	01/04/2001	J. Michael Salbaum	P-NI 4552	4685

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/754,997	SALBAUM, J. MICHAEL	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *1-8 and 16-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-15 and 20-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/10/05 has been entered.

2. Claims 1-42 are pending.

3. Claims 1-8 and 16-19 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 9-15 and 20-42 are under examination as they read on an isolated nucleic acid molecule of SEQ ID NO: 1 encoding Nope polypeptide of SEQ ID NO: 2 and SEQ ID NOs: 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 and oligonucleotides 300-325, 325-350 and 300-350 as the species.

5. The status identifier of claims 11 and 15 is wrong, i.e., "Withdrawn". It should be either "Previously presented or Original". Correction is required.

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Page 25, line 22 contains embedded hyperlinks and/or other forms of browser-executable code which are impermissible and require deletion.

7. 35 U.S.C. § 101 reads as follows:

> *"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".*

8. Claims 9-15 and 20-42 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the same reasons set forth in the previous Office Action mailed 8/10/04.

Applicant's arguments, filed 8/10/05, have been fully considered, but have not been found convincing.

Applicant asserts that the specification teaches a specific, substantial and credible utility. Applicant disagrees with the assertion in the previous Office Action mailed 8/10/04 on page 3, first paragraph, that the expression of Nope polynucleotides in the ventricular zone in the brain,

hippocampus, the pririform cortex, thalamic nuclei and foliae of the cerebellum does not mean that the polynucleotide is an appropriate target to regulate the development of the nervous system and related biological functions, as taught in the specification. The Office Action asserts that brain, hippocampus, the piriform cortex, thalamic nucleic and foliae of the cerebellum can express many polypeptides, such as constitutively expressed polypeptides, which are not appropriate targets. Applicant contends that the fact that these nerve tissues can express proteins that are not appropriate targets is irrelevant to Nope being an appropriate target. Applicant assets that the specification discloses that Nope is expressed in the developing mouse embryo in the notochord, in developing muscle tissues and in the developing nervous system (page 47, line 10, to page 48, line 16). Applicant further asserts that Nope expression is concentrated in the ventricular zone in the brain and in the hippocampus, the piriform cortex, thalamic nucleic and foliae of the cerebellum of adult brain (page 48, lines 3-16). Also Applicant submits that the specification discloses that Nope functions in cells of the nervous system that arise late in gestation (page 48, lines 8-1 1). Applicant asserts that the specification provides a clear and credible teaching of a functional role of Nope in neuronal development.

However, neither the instant specification or the art of record identifies even a single disease or disorder which has been shown to be associated with the NOPE proteins of the instant invention. It has not been shown that Nope is differentially expressed in any disease or disorder, the encoded polypeptide cannot be employed in a diagnostic capacity. Further, the "NOPE proteins" of the instant invention has not been shown to be associated with a particular physiological process which an artisan would wish to manipulate for clinical effect by the administration of the encoded protein or an agonist or antagonist thereof. Because an artisan does not know if an agonist-induced response by the encoded protein enhances or inhibits nervous system diseases.

Regarding Bardet-Biedl syndrome 4, Applicant submits that the mapping of Nope to a gene cluster of mouse chromosome 9, that is syntenic with a gene cluster of human chromosome 15 and the homology of Nope to human STS markers on human chromosome 15 corroborates Applicant's assertion of the utility of the claimed Nope polynucleotide. Applicant directs the Examiner's attention to the MPEP, 2 107.01 and MPEP page 2100-32. An example of a claim to a polynucleotide that does not satisfy the utility requirement is a polynucleotide with a disclosed use as a "gene probe" or "chromosome marker" "in the absence of a disclosure of a specific DNA target" (emphasis added). Applicant contends that in contrast to this example in the MPEP, the claimed Nope encoding nucleic acids map to a specific chromosome location on mouse clzromosome 9 that includes a gene cluster syntenic to chromosome 15, and the specification therefore clearly teaches a specific DNA target.

However, any genetic element (locus, allele, DNA sequence or chromosome feature) which can be readily detected by phenotype, cytological or molecular techniques, and used to follow a chromosome or chromosomal segment during genetic analysis can be used as chromosome marker. Therefore, the claimed utility as a chromosome marker that is linked to BBS4 is not specific. Further, the claimed Nope gene is a mouse gene and it is unclear how the mouse Nope polynucleotide would be used as a "specific DNA target" linked to human Bardel-Biedl syndrome 4.

Applicant submits that the immunoglobulin and fibronectin domains are well known structural motifs. While it is known that proteins with different sequences can fold similarly and have similar functions and can have similar functions with different structures, as asserted in the Office Action, Applicant is unaware of the basis for the assertion in the Office Action on page 4 that proteins with very similar sequence fold up differently and respectfully request that the Examiner provide evidence that proteins with very similar sequences fold differently. Even so, the immunoglobulin and fibronectin domains are well characterized structural domains present on cell surface receptors and diffusible ligands that function as binding domains (page 12, line 7, to page 14, line 29). A subgroup of the immunoglobulin superfamily has been associated with migration and guidance of axonal growth cones (page 13, line 1, to page 14, line 29). Applicant disagrees with the assertion in the Office Action on page 4 that functional relatedness is not credible in the face of evidence in the art that structurally related polypeptides are frequently dissimilar functionally. To the contrary, Applicant respectfully submits that the teachings of the specification support a function and credible utility.

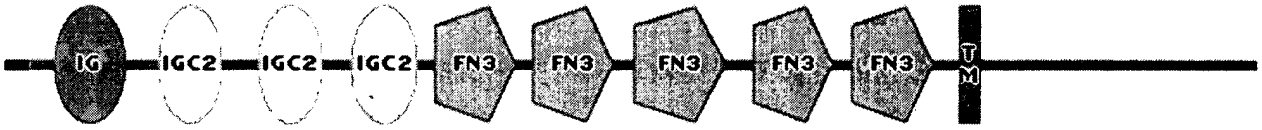
Regarding the requested evidence that proteins with very similar sequence fold up differently and respectfully request that the Examiner provide evidence that proteins with very similar sequences fold differently. The Examiner provides Alexandersson lecture titled Pairwise sequence alignment (http://www.fcc.chalmers.se/~marina/files/BioII_Pairwise_2003.pdf, 2003), as evidence that proteins with very similar sequence fold up differently (see page 1, in particular). Further, sequence similarity does not always means similar folding and function.

Further, the immunoglobulin superfamily (IgSF) is a heterogenic group of proteins built on a common fold, called the Ig fold, which is a sandwich of two beta sheets. Although members of the IgSF share a similar Ig fold, they differ in their tissue distribution, amino acid composition, and biological role. Rougon et al (Annu Rev Neurosci. 2003;26:207-38. 2003) teach that immunoglobulin superfamily (IgSF) proteins are implicated in diverse steps of brain development, including neuronal migration, axon pathfinding, target recognition and synapse formation, as well as in the maintenance and function of neuronal networks in the adult. Rougon *et al* illustrate that the complexity of IgSF protein function results from various different levels of regulation including regulation of gene expression, protein localization, and protein interactions. Since the IgSF differ in their tissue distribution and biological role, this utility is neither specific nor substantial. The rejection is based on the failure to disclose sufficient properties of the NOPE protein to support an inference of utility. The Ig superfamily to which the NOPE polypeptide belongs is a family in which the members have divergent functions based on which tissues the protein is expressed. Assignment to this family does not support an inference of utility because the members are not known to share a common utility.

The instant situation is directly analogous to that which was addressed in *Brenner V. Manson*, 148 U.S. P. Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this

term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S. C. § 101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility.

However, no single effect of the disclosed Nope protein is ascribed to the claimed protein. Therefore, the original members of the family were not classified based on their biological activity, but rather, by their common structure and the fact that the expression of Nope polynucleotides in the ventricular zone in the brain, hippocampus, the pririform cortex, thalamic nuclei and foliae of the cerebellum. Without some common biological activity for the family members, a new member would not have a specific or substantial utility when relying only on the fact that it has structural similarity to the other family members and is also expressed on the surface of the cells. The members of the family have different biological activities, but there is no evidence that the encoded polypeptide share any one of those different activities. That is, no activity is known to be common to all members. To argue that all the members can be used for "regulation" or modulation of nervous system is to argue a general, nonspecific utility that would apply to virtually every member of the family, absent evidence to the contrary.



With respect to the reference by Marg et al., Applicant submits that this reference corroborates Applicants assertion that immunoglobulin domains are conserved and function in binding. Applicant submits that Marg et al teach that the short and long form of neurotractin do share similar functions in that they bind to CEPU-1 and LAMP. Applicant asserts that while the long and short form of neurotractin have different affinities for CEPU-1 and LAMP, does not change the shared function of binding to the short and long form of neurotractin to the same ligands. Applicant concludes that Marg et al corroborates Applicant's position that the immunoglobulin domains are well characterized binding domains that one skilled in the art would understand to have a predictable function in binding, even if the specific binding partner is not known.

However, Marg et al teach that the most diversified class of molecules that is involved in contact-dependent regulation of neurite outgrowth and axon guidance are the neural members of immunoglobulin superfamily (IgSF). Further, Marg et al teach that these proteins show complex and promiscuous extracellular interactions which appears to be a common feature of contact dependent cell surface molecules implicated in axon guidance (see page 865, 1st col., last paragraph to 2nd col., 1st paragraph). Importantly, Marg et al concluded that the biological functions of the neurotractin-CEPU-1 or the neurotractin-LAMP interactions are currently unknown (see page 873, 2nd col., 2nd, 1st paragraph). Therefore, the interaction of neurotractin-

CEPU-1 has nothing to do with its function as mediator of adhesion and neurite initiation of telencephalic neurons and hence consider irrelevant to the utility of neurotractin function in promoting neurite outgrowth. Further, while the guidance cues for the encoded NOPE polypeptide is not known, it is unpredictable whether binding to a ligand would elicit an attractive or repulsive response.

Applicant directs the Examiner's attention to the utility guidelines under comment 19. In particular, applicant pointed that "a rigorous correlation" need not be shown in order to establish a practical utility: "reasonable correlation is sufficient". Further, Applicant pointed to the statement that "when a class of proteins is defined such that the members share a specific, substantial and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein".

The fact pattern indicates that there is no reason to doubt that the encoded NOPE protein is a member of the IGSF of proteins and that different IGSF are important to a wide variety of physiological processes. However, assignment to a prior art family of proteins is generally insufficient to meet the utility requirement unless such assignment would allow the artisan to assign a specific and substantial use to the new member of the proteins family. Because there is no indication of a specific and substantial use for the claimed member of IGSF of proteins, this encoded protein does not comply with the utility requirement of 35 U.S.C. 101. However, objective evidence might overcome this rejection if it supports an assertion that one of ordinary skill in the art would recognize that each member of the IGSF protein family would have been reasonably expected to have a particular specific and substantial function or activity.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 9-15 and 20-42 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Further, the specification does not provide sufficient enablement for how to make any nucleic acid molecule encoding a Nope polypeptide of SEQ ID NO: 2 and having a "Nope polypeptide activity" or "modification" of the encoding nucleic acid sequence or a "modification" of SEQ ID NO:1 in claims 9-10; a kit comprising one or more Nope oligonucleotides consisting of the anti-sense strand of Nope oligonucleotides of SEQ ID NO: 1 in claims 20-24. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 8/10/2004.

Further, the use of antisense forms of Nope nucleic acids, as disclosed in the specification at page 26, lines 13-16 that antisense reagents can be advantageously used to block transcription of Nope RNA in cell, or in other applications known to those skilled in the art in which hybridization to a Nope nucleic acid molecule is desirable. However, such "therapeutic methods" is well known in the art to be highly unpredictable, even though the level of skill in the art is high. For instance, Mountain reviews in TIBTECH (18:119-128 2000) that while much progress has been made in the field of gene therapy, developing effective gene therapies is much more demanding than originally anticipated (e.g., pg 120, middle); and that most of the difficulty lies with the development of effective vectors since the vectors in use all have both advantages and disadvantages (e.g., Table 4). Mountain concludes that it is unlikely that a universal vector will emerge in the next few years (page 125, middle of 1st column). Similarly, although antisense therapy has progressed in recent years, there is still a high level of unpredictability in the art. This unpredictablity was summarized recently by Branch (TIBS 1998; 23:45-50). In particular, difficulties in ensuring that the oligo interacts with its single gene target versus other genes, and a variety of unexpected non-antisense effects, complicate the use of antisense compounds (e.g., summarized in Abstract). Thus in the absence of working examples or detailed guidance in the specification, the intended uses of an antisense nucleic acid are fraught with uncertainties.

Applicant's arguments, filed 8/10/05, have been fully considered, but have not been found convincing.

Applicant points to the specification on pages 9 and 24-25 for support that a modification of a nucleic acid can include one or several nucleotide additions, deletions or substitutions with respect to reference sequence, including a substantially the same nucleotide sequence that can hybridize under moderately stringent or higher stringency conditions.

However, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of encoded peptides/polypeptide broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in the encoded polypeptide's/peptide's amino acid sequence and still retain similar biological activity requires a knowledge of and guidance with regard to which amino acids in the encoded protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly in tolerant to modification), and detailed knowledge of the ways in which the encoded protein's structure relates to the function. However, the problem of predicting the encoded protein structure from mere sequence data of a single nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain function aspects of the encoded protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

Further, there is tremendous variability in the importance of individual amino acids in protein sequences. Since the Fn and Ig domains are a key determinants of activity of Nope protein, residue substitutions that are conservative (e.g., Glu in equilibrium Asp, Asn in equilibrium Asp, Ile in equilibrium Leu, Lys in equilibrium Arg and Ala in equilibrium Gly) can have severe phenotypic effects. There is no simple way to infer the likely effect of an amino acid substitution on the basis of sequence information alone. Therefore, one skill in the art would not be able to predicted what nucleic acid residue substitutions can be replaced which leads to tolerant modification in the encoded Nope polypeptide.

11. Claims 9-10 and 14 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Action mailed 8/10/2004.

Applicant's arguments, filed 8/10/05, have been fully considered, but have not been found convincing.

Applicant argues that with regard to the term "modification," the specification teaches that a modification of a nucleic acid can include one or several nucleotide additions, deletions or substitutions with respect to a reference sequence, including a substantially the same nucleotide sequence that can hybridize under moderately stringent or higher stringency conditions (page 9, lines 16-30). The specification also teaches various stringency conditions (page 24, line 15, to page 25, line 18). Therefore, Applicant respectfully submits that the specification provided sufficient description and guidance to enable the claimed nucleic acid molecules and modifications thereof.

However, neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (modified Nope) to describe the claimed genus, nor does it provide a description of structural features that are common to species (of modified Nope). The specification provides no structural description of Nope other than ones specifically exemplified; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed modifications looks like. The specification's disclosure is inadequate to describe the claimed genus of a modification of the encoding Nope nucleic acid sequence.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

September 6, 2005

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